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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,309	06/21/2001	Melissa K. Carpenter	090/002	9525

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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/888,309	CARPENTER ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-48* is/are pending in the application.

4a) Of the above claim(s) *23-33,47 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The preliminary amendment filed February 19, 2002 has been entered. Claims 1-22 have been cancelled and Claims 23-36 have been newly added.

The preliminary amendment filed November 6, 2003 has been entered. Claims 34-36 have been amended. Claims 37-48 have been newly added.

Accordingly, Claims 23-48 are pending in the instant application.

Applicants' election with traverse of Group IV, Claims 34-36, in the response filed November 6, 2003 is acknowledged. The elected invention is drawn to a system of two cultured cell populations. Newly added Claims 37-46 are directed to the invention of Group IV. Newly added Claim 47 is directed to the invention of Group II. Newly added Claim 48 is directed to the invention of Group III.

Claim 23-33, 47, and 48 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicant timely traversed the restriction requirement in the response filed November 6, 2003. Applicants traverse the restriction requirement between Groups I, II, and III. Applicants argue that the inventions of Groups II and III are actually methods for producing a neural cell population. Therefore, Applicants conclude, upon determination that Claim 23 is free of the prior art, then Claims 32 and 33 will also be free of the prior art, and there is no burden in examining claims 23-33 together. In response to Applicants' argument that the inventions of Groups II and III are actually methods for producing a neural cell population, this clearly is not true as the methods recited in the claims require much more than producing a neural cell population; the methods involve carrying out a wide variety of assays to assess the effect of a compound on the function of a cell population or assaying the cell population and preparing a polynucleotide comprising a polynucleotide sequence expressed in the cell population. Applicant is reminded that distinctness is not determined by claim format but rather by the relationship between the different inventions. In the instant case, inventions I-III

are drawn to materially different methods that require different starting materials, different modes of operation, and produce different effects. In response to Applicants' argument that upon determination that Claim 23 is free of the prior art, then Claims 32 and 33 will also be free of the prior art, Applicants are reminded that the examination process requires that the Examiner make no assumption that Claim 23 is free of the art. Moreover, being free of the prior art does not mean that an invention is patentable. Each of the inventions of Groups I-III requires consideration of separate issues relating to assessment of novelty, obviousness, utility, written description, and enablement. Furthermore, the searches for the inventions of Groups I-III are not coextensive. Thus, search and examination of all 3 or 4 inventions in a single patent application constitutes a serious burden on the Examiner.

Claims 34-46 are examined herein.

Specification

The disclosure is objected to because it contains embedded hyperlinks and/or other forms of browser-executable code. See page 19, line 4 and page 22, line 19. Applicant is required to delete the embedded hyperlinks and/or other forms of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description/New Matter

Claims 34-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants are referred to the final guidelines on written description published January 5, 2001 in the Federal Register at Volume 66, Number 4, pp. 1099-1111 (also available at www.uspto.gov).

The claims recite combinations without support in the original disclosure, thereby adding new matter to the claims.

The newly added claims recite **a system comprising two cell populations.** Claim 34 is directed to a system for producing differentiated cells from human embryonic stem (hES) cells, comprising:

a first cell population comprising undifferentiated hES cells; and

a second cell population comprising progeny of the hES cells in a medium containing one or more added TGF-β superfamily antagonists.

Claim 35 is directed to a system for producing differentiated cells from human embryonic stem (hES) cells, comprising:

a first cell population comprising undifferentiated hES cells; and

a second cell population, comprising at least ~10% hES-derived neural cells, identifiable by the criteria that they are progeny of said hES cells and express both MAP-2 and tyrosine hydroxylase. However, the new claims are not supported by the original disclosure because the original disclosure does not specifically contemplate this combination of two cell populations. At page 5 of the preliminary amendment (filed 11/6/03), Applicants refer to page 4, lines 34-35 of the specification as providing support for the new claims. The cited lines read "[t]his invention provides a system for efficient production of differentiated cells from primate pluripotent stem (pPS) cells." However, this section only provides support for certain elements of the claims and does not provide specific support for the combination of two cell populations now being claimed. The Examiner has carefully reviewed the entire specification and does not find support for the claimed invention as a whole. Applicants have not pointed to specific support for the new claims in the specification as-filed.

Thus, the amendment introduces new matter into the claims.

Enablement

Claims 34-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary.

The following factors have been considered.

Nature of the invention. The claims are directed to a system comprising two cell populations. As claimed, the two cell populations are intended to be used together somehow. However, the specification does not specifically disclose how to use these two cell populations together. The specification contemplates that the cells of the invention can be used in drug screening. However, the specification does not disclose how one would use the claimed **system of two cell populations** in drug screening. The specification also discloses that the cell populations are intended to be used for therapeutic transplantation (see the specification at page 24, lines 20-22). The specification states that "[c]ells prepared according to this invention that are useful for human or veterinary therapy are optimally supplied in a pharmaceutical composition ..." (page 25, lines 5-6). The specification contemplates using a variety of differentiated cell types, such as neural cells, cardiomyocytes, and hepatocytes, for therapeutic transplantation (page 24, lines 19-41). However, the specification does not address how to

use the **system of two** cell populations. As discussed above, the specification does not specifically contemplate a **system of two** cell populations as claimed.

Amount of direction or guidance presented and the presence or absence of working examples. The specification discloses in Example 5 the testing of various factors for use in the differentiation of hES cells to neurons. However, none of the examples demonstrate the use of the claimed **system of two cell populations.** As discussed above, the specification does not contemplate a **system of two** cell populations as claimed. Thus, the specification does not adequately teach how to use the claimed compositions. Furthermore, none of the examples demonstrate a therapeutic use of the system of two cell populations.

The specification contemplates using the various "differentiated cells of this invention" to screen candidate compounds or environmental conditions that affect differentiation or metabolism of a cell type of interest" (page 5, lines 36-37). Again however, the specification does not provide any guidance for using the claimed **system of two** cell populations in drug screening assays. The specification must provide specific guidance for the use of the **claimed** compositions. Here it does not.

It is not to be left up to the skilled artisan to figure out how to use the claimed compositions. The courts held that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner et al.* 166 USPQ 138 (CCPA 1970). With regard to the differentiated cells described in the specification, this specification only teaches what is intended to be done and how it is intended to work, but does not actually teach how to do that which is intended. With regard to the **claimed** compositions, the specification does not provide any guidance for their use.

State of the prior art and predictability of the art. The state of the art is such that very little is known about the cell types that can be used to restore neurological function. One of the lingering questions in the field of stem cell research relates to the stage of differentiation of stem cells useful for

transplantation and whether the same stage will be useful for all transplantation applications, or vary on a case-by-case basis (see p. ES-8, column 1 of Stem Cells: Scientific Progress and Future Research Directions, June 2001).

In a review of the state of the art of stem cell technology, the National Institutes of Health acknowledge the potential usefulness of stem cells in theraeutic transplantation and the possible development of therapeutic protocols in the future (see Stem Cells: Scientific Progress and Future Research Directions, June 2001). However, the review also illustrates that there are numerous and significant obstacles that must be overcome. As such, the asserted utility of the present invention, directed to using the claimed compositions in therapeutic transplantation constitutes a credible utility, albeit one that is not enabled by the instant specification. The instant rejection therefore is not for lack of utility, but rather for lack of enablement for the asserted utility. Furthermore, the asserted utilities of therapeutic transplantation or drug screening are the only utilities disclosed for the differentiated cells referred to in the specification. However, the specification does not provide specific guidance for the use of the **claimed** compositions (the system of two cell populations). With regard to therapeutic transplantation, there is no teaching at all for using the claimed combinations of cell populations in therapeutic transplantation. With regard to drug screening, there is no teaching at all for using the claimed combinations of cell populations in drug screening assays. For the reasons discussed herein, the specification does not teach how to use the **claimed** compositions for the utilities contemplated for the **differentiated cells** referred to in the specification.

The specification fails to provide an enabling disclosure for using the claimed compositions in accordance with the utilities asserted in the specification for differentiated cells (*i.e.*, for drug screening or therapeutic transplantation). The utilities asserted in the specification are directed to uses for precursor cells and terminally differentiated cells, but not to the specific combination of cell populations instantly claimed.

The specification fails to provide an enabling disclosure for using the claimed compositions to provide a therapeutic benefit because the specification does not provide **specific guidance** regarding how to use the claimed compositions therapeutically. In unpredictable arts, it is the specification itself that must provide the novel teachings for using the claimed compositions therapeutically. The specification does not offer any guidance as to how the claimed compositions could be used therapeutically for the treatment of any disorder. No working examples demonstrate a therapeutic effect in a diseased animal upon transplantation of the claimed compositions. The specification contemplates that "cells of the invention" can be used therapeutically. Accordingly, the specification must teach how to use the claimed compositions in transplantation protocols to produce a therapeutic effect. However, the specification does not teach how to produce a therapeutic effect in any animal. The specification fails to provide any guidance relating to the amount of cells to inject, the site of injection, and extent of cellular persistence required to provide any therapeutic benefit for any disorder. There are no teachings regarding the administration of the two separate cell populations recited in the claims. There is no guidance relating to the order of administration of the two cell populations, the physical location for implantation of each cell population, or the route of administration for the two cell populations, whether the same or different.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

Given the limited working examples, the limited guidance provided in the specification, the lack of any showing of therapeutic benefit upon transplantation of the claimed compositions, the lack of any use for the claimed compositions in drug screening assays, the broad scope of the claims, and the unpredictability for producing a therapeutic effect upon transplantation of the claimed compositions (consisting of a system of two cell populations), undue experimentation would have been required for one

skilled in the art to use the claimed compositions in methods of transplantation to produce a therapeutic effect or in drug screening assays.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 36-40 are indefinite in their recitation of "claim 23" because claim 23 is withdrawn from consideration.

Claims 36-40 are indefinite in their recitation of the parenthetical phrase "(or their progeny)" because it is unclear if the parenthetical matter is an actual claim limitation or merely descriptive.

Claim 38 is indefinite in its recitation of "oaf" because it appears to be a typographical error.

Claims 34-46 are indefinite in their use of various abbreviations, such as "TGF-β" and "MAP-2". All names should be completely spelled out where they first appear in the claims, followed by the abbreviation in parentheses. Subsequent use of the abbreviation only is then permitted.

Claim 46 is indefinite because it depends from itself.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to William Phillips, whose telephone number is (571) 272-0548.

Anne-Marie Falk, Ph.D.

Anne-marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER